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R E M A R K S

Claims 8-16 are pending in the application. Claims 8-16 are rejected under 35 U.S.C. § 112, first paragraph. Claims 9-15 are rejected under 35 U.S.C. § 103. Applicants have amended claims 8, 9 and 16 to more particularly point out and distinctly claim the invention. No new matter is introduced by the new claims and the claims are fully supported by the instant specification. For reasons detailed below, the rejections should be withdrawn and the claims allowed to issue. Entry of the foregoing amendments is respectfully requested.

1. Miscellaneous

The Examiner has indicated that new claims 8-15 have been misnumbered. However, a review of the application filed on August 16, 2000 indicates that the application was filed with claims numbered 1-7 (See Exhibit A). As claims 1-7 were deleted, any new claims added by amendment should begin with claim 8. Therefore, Applicants have correctly numbered the claims. In view of the correct numbering of the claims, the claim dependency is correct.

Due to a typographical error new claim 9 was misnumbered as claim 8. This error has been corrected by amendment herein.

2. The Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 7-15 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention.

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According to the Examiner, claims 7 and 8 are vague, indefinite and confusing in the recitation "wherein said microorganisms express an enzyme which is capable of reducing a carbonyl function", since the mere "capability" is not sufficient to carry out the reaction. In addition, the reaction requires more than "reducing a carbonyl function", since this reaction produces an optically active product, and reduction has to occur at a specific carbonyl group to produce the required product.

In response, Applicants have amended claim 8 to indicate that the trifluoroacetic acid derivatives of formula II are enantioselectively reduced using microorganisms of the genus *Escherichia*, or cell-free extracts derived therefrom, to produce the specified 4,4,4-trifluoro-3(R)-hydroxybutyric acid derivatives.

The Examiner alleges that the antecedent basis for "said trifluoro ... acid derivatives" is uncertain, since other than the preamble there is no indication of a product formed and recommends that the phrase be amended to read, -- isolating the trifluoro ... acid derivatives produced--. In response, Applicants have amended claim 8 as suggested by the Examiner.

The Examiner maintains that claims 9, 10, 11 and 12 are incomplete in depending on themselves. In addition, claims 12 and 14 are objected to as being in improper form because a multiple dependent claim may not depend on other multiple dependent claims.

Applicants have amended claim 9 to correct the typographical error designating the claim as claim 8. Given the correct numbering of the claims, claims 12 and 14 do not depend on multiple dependent claims, thus, they are in proper form

The Examiner asserts that the limitations of claim 16 are not understood, since there is only one claim 11.

Applicants have amended claim 16 to delete the phrase "one of."

In view of the amendment to the claims, Applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

3. The Claims are not Obvious

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kula *et al.* (U.S. Patent No. 5,523,223; "Kula") taken with Kita *et al.* (1996, Applied and Environmental Microbiology 62:2303-2310; "Kita") and Texidre et al. (EP0736606 A1; "Tixidre").

According to the Examiner, Kula teaches a process for the production of 3(R)-hydroxybutyric acid derivatives using a microbial strain having reductase activity. The Examiner maintains that although the reference differs from the claimed invention in that it does not use an *E. coli* strain transformed with a gene coding for a suitable reductase, Kita teaches the production of an *E. coli* strain transformed with a gene coding for a reductase which is suitable for converting related 3-(R)-hydroxybutyric acid derivatives.

The Examiner alleges that one of ordinary skill in the art would have had a reasonable expectation of success in obtaining 4,4,4 trifluoro-3(R)-hydroxybutyric acid derivatives using the microbial strain having reductase activity as taught by Kula and Kita. Further, one of ordinary skill in the art would have had been motivated at the time the claimed invention was made to produce the trifluoro derivatives of 3(R)-hydroxybutyric acid in view of the teachings of Tixidre regarding the utility of such compounds as intermediaries in the

production of befloxatone, a compound having important pharmaceutical activity as a reversible and selective monoamine oxidase-A inhibitor.

A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re Ofarrell* 853 F.2d 894 (Fed. Cir. 1988).

As argued by Applicants in their response filed August 4, 2003, the present invention is not rendered obvious by the cited references either alone, or in combination, for the following reasons.

First, Kula describes a reductase from *Canidida parapsilosis* having an extremely broad substrate spectrum. Based on the unpredictability of biological systems, one skilled in the art would not have had a reasonable expectation that such a reductase of *Canidida parapsilosis* could be successfully cloned and expressed in *E.coli*.

Second, although Kita describes microorganisms of the genus *Escherichia* transformed with a gene encoding a reductase from *Sporobolomyces salmonicolor*, Kita only demonstrates the use of the substrate ethyl 4-chloro-3-oxobutanoate. Kita fails to demonstrate that such a reductase is capable of enantioselectively reducing the trifluoroacetic acid derivatives of formula II as specified in claim 1.

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Applicants respectfully submit that none of the cited references, alone or in combination, disclose or suggest a strain of *E. coli* capable of enantioselectively reducing the trifluoroacetic acid derivatives of formula II to yield the trifluoro-3R-hydroxybutyric acid derivatives of formula I, therefore, the claimed process for preparing such acid derivatives using such strains of *E.coli* simply cannot be rendered obvious. Specifically, Applicants assert that neither Kita, nor Kula, either alone or in combination disclose or suggest, a process comprising the step of reacting a trifluoroacetic acid derivative of formula II with a microorganism of the genus *Escherichia* expressing an enzyme which *enantioselectively* reduces the trifluoroacetic acid derivative of formula II to yield a trifluoro-3R-hydroxybutyric acid derivatives of formula I.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

Entry of the foregoing remarks into the file history of the above identified application is respectfully requested. Applicant believes that the invention described and defined

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by the claims is patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

Dated: January 6, 2004

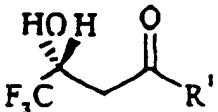


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1. Process for preparing trifluoro-3(R)-hydroxybutyric acid derivatives of the general formula



I

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in which

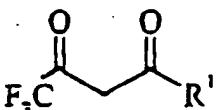
R¹ is -OR², in which R² is hydrogen, C₁₋₁₀-alkyl, C₁₋₁₀-alkenyl, C₃₋₈-cycloalkyl, aryl, alkoxyalkyl or alkoxyalkoxyalkyl,

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-NR³R⁴, in which R³ and R⁴ are identical or different and represent hydrogen, C₁₋₁₀-alkyl, C₁₋₁₀-alkenyl, C₃₋₈-cycloalkyl or aryl, or -SR⁵, in which R⁵ is hydrogen, C₁₋₁₀-alkyl, C₁₋₁₀-alkenyl, aryl or C₃₋₈-cycloalkyl,

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which process comprises reacting a trifluoroacetoacetic acid derivative of the general formula



II

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in which R¹ has the said meaning, using microorganisms which are capable of reducing a carbonyl function or using a cell-free enzyme extract of these microorganisms.

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2. Process according to Claim 1, characterized in that the biotransformation is carried out using microorganisms of the genus Escherichia which are transformed with a gene which encodes an enzyme which is capable of reducing a carbonyl function.

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3. Process according to Claim 2, characterized in that the biotransformation is carried out using microorganisms of the species Escherichia coli JM109, Escherichia coli HB 101 or Escherichia coli DH5 which are transformed with a gene which encodes an enzyme which is capable of reducing a carbonyl function.

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4. Process according to one of Claims 1 to 3, characterized in that the biotransformation is carried

out using microorganisms of the species Escherichia coli JM109, Escherichia coli HB101 or Escherichia coli DH5 which are transformed with genes which encode both an enzyme which is capable of reducing a carbonyl 5 function and a glucose dehydrogenase.

5. Process according to Claim 4, characterized in that the biotransformation is carried out using microorganisms of the species Escherichia coli JM109 or the species Escherichia coli DH5 which are transformed 10 with the plasmids pKAR and pKKGDH, as deposited under the deposition numbers DSM 11902 and DSM 12566, respectively.

6. Process according to one of Claims 1 to 5, characterized in that the biotransformation is carried 15 out a temperature of from 5 to 60°C.

7. Process according to one of Claims 1 to 6, characterized in that the biotransformation is carried out at a pH of from 5 to 10.